Tohoku J. Exp. Med., 2025, **266**, 37-46

Assessment of Clinicopathological Characteristics and Clinical Outcomes of Patients Who Developed Non-Muscle-Invasive Bladder Cancer After Radiotherapy for Prostate Cancer: A Retrospective Multicenter Study

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Radiotherapy for prostate cancer may induce the development of secondary bladder cancer. However, the clinicopathological characteristics and clinical outcomes of this entity have not been fully elucidated. Therefore, this study compared the clinicopathological characteristics and clinical outcomes of patients who developed secondary bladder cancer after radiotherapy with those of controls. The medical records of patients newly diagnosed with non-muscle-invasive bladder cancer were retrospectively analyzed. Newly diagnosed non-muscle-invasive bladder cancer that developed ≥ 5 years after radiotherapy for prostate cancer was defined as secondary non-muscle-invasive bladder cancer during this study. Patients with newly diagnosed non-muscle-invasive bladder cancer who did not meet this criterion were included in the control group. The clinicopathological characteristics and recurrence-free survival rates of patients with secondary non-muscle-invasive bladder cancer were compared with those of controls. A total of 26 (2.6%) of the 1,019 patients from the Tohoku Urological Evidence-Based Medicine Study Group and Kyoto University Hospital who were screened met this criterion for secondary non-muscle-invasive bladder cancer. Clinicopathological characteristics were similar between the secondary non-muscle-invasive bladder cancer and control groups, except for sex and age. Propensity score-matched analysis revealed that the recurrence-free survival rates of patients with secondary non-muscle-invasive bladder cancer may not be poorer than those of control patients. Tumor characteristics and recurrence-free survival rates of patients with secondary non-muscle invasive bladder cancer were comparable with those of controls. Further large-scale studies should be conducted to clarify the tumor characteristics and clinical outcomes of these patients after radiotherapy.

Keywords: clinical outcome; non-muscle-invasive bladder cancer; prostate cancer; radiation-induced malignancy; secondary bladder cancer
Tohoku J. Exp. Med., 2025 May, **266** (1), 37-46.
doi: 10.1620/tjem.2024.J109

Received July 27, 2024; revised and accepted October 3, 2024; J-STAGE Advance online publication October 17, 2024
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Introduction

The numbers of patients with cancer and survivors of cancer have increased in the past decades and are expected to continue to increase in the future (Travis et al. 2006; Morton et al. 2014; Huang and Zhou 2020). Survivors of cancer are at risk of developing secondary malignancies, which are severe late effects of treatment (including radiotherapy [RT] and chemotherapy) for the primary malignancies. Moreover, these patients are at a higher risk for non-relapse-related mortality (Chao et al. 2019; Demoor-Goldschmidt and de Vathaire 2019).

Studies of survivors of atomic bombings have revealed that radiation exposure is associated with the risk of developing malignancies (Doll 1995). However, a prolonged latency period (usually ≥ 5 years) has been observed between radiation exposure and the development of malignancies. RT for malignancies and non-oncologic diseases can also induce the development of secondary malignancies. The histological types of these secondary malignancies, known as radiation-induced malignancies, differ from those of primary diseases (Braunstein and Nakamura 2013). Malignancies that develop after RT for primary malignancies are considered secondary (radiation-induced) malignancies if they meet the following criteria: (i) they arise within the irradiated field; (ii) they differ histologically from the primary malignancy; (iii) they were not evident during RT; and (iv) they have a latency period between RT and their development (usually ≥ 5 years). Malignancies that develop < 5 years after RT for primary malignancies are not categorized as radiation-induced malignancies (Murray et al. 2014). Nevertheless, a clear, internationally standardized definition of secondary malignancies has not yet been established.

RT, which is an essential part of oncologic therapy, plays an important role in the treatment of prostate cancer (Huang and Zhou 2020). Previous registry-based studies have shown that patients with prostate cancer who received RT may be at high risk for developing subsequent bladder cancer (Wallis et al. 2016). Furthermore, several registry-based studies that compared differences in the incidence of subsequent bladder cancer according to the type of treatment administered for prostate cancer suggested that patients with prostate cancer who received RT are at a higher risk of developing subsequent bladder cancer than those who underwent surgery alone (Murray et al. 2014). However, most of these studies included patients who developed bladder cancer < 5 years after RT.

Radiation-induced malignancies are potentially aggressive, and they may be associated with a poorer prognosis than that of the corresponding primary malignancies (Khanna et al. 2021). The clinical outcomes and clinicopathological characteristics of patients with subsequent bladder cancer, including secondary bladder cancer, have not been sufficiently investigated.

Therefore, this study defined newly diagnosed non-muscle-invasive bladder cancer (NMIBC) that developed ≥ 5 years after RT for prostate cancer as secondary NMIBC and compared the clinicopathological characteristics and recurrence-free survival (RFS) of patients with secondary NMIBC with those of control patients.

Materials and Methods

Ethics statements

This retrospective study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine, Sendai, Japan (approval number: 2018-1-450), and it adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained via an online opt-out process.

Study design and population

The medical records of patients who underwent transurethral resection of bladder tumor (TURBT) between January 2009 and December 2016 at 10 institutions that participated in the Tohoku Urological Evidence-based Medicine Study Group and Kyoto University Hospital were retrospectively analyzed (Sato et al. 2023). Data of patients newly diagnosed with NMIBC who received definitive therapy (radical cystectomy or RT), those newly diagnosed with NMIBC who had been followed-up for ≥ 3 years and did not experience disease recurrence or progression, and those newly diagnosed with NMIBC who had been followed-up for ≥ 3 months at the time of recurrence or progression were analyzed. Patients with muscle-invasive bladder cancer (MIBC), non-urothelial carcinoma, recurrent tumors, distant or lymph node metastases, or a history of upper tract urothelial carcinoma (UTUC) were excluded from this study.

Data collection

The study variables included age, sex, tumor stage, tumor grade, presence of carcinoma in situ (CIS), tumor multiplicity (single or multiple), largest tumor diameter (< 3 or ≥ 3 cm), and the 2019 European Association of Urology (EAU) risk group of the patients at the time of initial TURBT. Patients who were newly diagnosed with NMIBC ≥ 5 years after RT for prostate cancer and those who were newly diagnosed with NMIBC but did not meet the aforementioned criterion (for secondary NMIBC) were defined as patients with secondary NMIBC and control patients, respectively. In the present study, patients newly diagnosed with NMIBC < 5 years after RT for prostate cancer were defined as the control after RT group and included in the control group.

Recurrence was defined as intravesical recurrence of cancer after the initial TURBT. Progression was defined as the development of muscle-invasive disease (stage T2 or higher) and metastasis to the lymph nodes or other distant organs. The duration between RT for prostate cancer and the bladder cancer diagnosis was evaluated. The clinicopathological characteristics of the secondary NMIBC and

control groups were analyzed. Furthermore, the percentages of patients in the secondary NMIBC and control groups who received adjuvant intravesical therapy or underwent a second transurethral resection (TUR) were calculated. The RFS rates of patients in the secondary NMIBC and control groups were compared. RFS was calculated as the duration between the initial TURBT and the first recurrence (the date when recurrence was confirmed histologically). Patients with NMIBC who experienced progression and those who received definitive therapy were not included in the RFS calculations.

Statistical analysis

Continuous and categorical variables were presented as the median and interquartile range (IQR) and the absolute number and percentage, respectively. The RFS rates of the two groups were estimated and compared using the Kaplan-Meier method with the log-rank test. Categorical variables were compared using Pearson's chi-square test. Propensity-score matching of patients in the secondary NMIBC and control groups was performed using the following clinicopathological variables: age, sex, tumor stage, tumor grade (World Health Organization [WHO] 2004/2016), presence of CIS, tumor multiplicity, and largest tumor diameter. Patients in the secondary NMIBC group were matched with those in the control group using 1:2 ratio. The predictors of RFS for patients in the combined population of the secondary NMIBC and control groups were identified using the Cox proportional hazards model. Statistical significance was considered as $P < 0.05$. All statistical analyses were performed using EZR (version 1.61; Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R software (version 4.2.2) (Kanda 2013).

Results

Among the 1,019 patients from 11 institutions who were screened, only 26 (2.6%) met the criterion for secondary NMIBC defined in this study. The median duration between RT for prostate cancer and NMIBC development was 8 years (IQR, 7-10 years; range, 5-12 years). In the secondary NMIBC group, 25 (96.2%) patients underwent external beam RT (EBRT), and one (3.8%) underwent brachytherapy alone. The median ages of the patients in the control group at the time of initial TURBT and in the secondary NMIBC group were 71 years (IQR, 63-78 years) and 79 years (IQR, 74-83 years), respectively. In the control group, 19 (1.9%) patients received definitive therapy and 22 (2.2%) experienced disease progression. However, in the secondary NMIBC group, no patient experienced disease progression and no patient received definitive therapy. Table 1 presents the clinicopathological characteristics of patients in the secondary NMIBC and control groups. Significant differences in age and sex, but not in tumor stage, tumor grade, presence of CIS, tumor multiplicity, or largest tumor diameter were observed between groups. Table 2 presents the proportions of patients in the secondary NMIBC and control groups who received adjuvant intravesical therapy and underwent a second TUR. Significant differences were not observed in the ratios of patients who received these therapies between groups. Table 3 presents the proportions of patients with secondary NMIBC and propensity score-matched control patients who received adjuvant intravesical therapy and underwent a second TUR. Significant differences in the ratios of patients who received these therapies were not observed between groups.

Seven (26.9%) and 334 (35.1%) patients in the secondary NMIBC and control groups, respectively, experienced disease recurrence during a median follow-up duration of 50 months. Fig. 1 presents the RFS rates of patients in the secondary NMIBC and control groups. Significant differences in RFS between groups were not observed ($P = 0.38$). Fig. 2 presents the RFS of the patients in the secondary NMIBC and control groups after the propensity score-matched analysis. Significant differences were not observed in RFS between patients in the secondary NMIBC group and propensity score-matched patients in the control group ($P = 0.29$). Fig. 3 presents the RFS rates of patients in the secondary NMIBC and control after RT groups ($n = 12$). Significant differences were observed in RFS between groups ($P = 0.015$). A multivariate Cox proportional hazards regression analysis of the combined population of the secondary NMIBC and control groups ($n = 978$) revealed that age (≥ 70 years), tumor multiplicity (multiple), and largest tumor diameter (≥ 3 cm) were significantly associated with poorer RFS. However, a history of RT for prostate cancer ≥ 5 years before the development of NMIBC was not associated with RFS (hazard ratio [HR], 1.13; $P = 0.79$) (Table 4).

Discussion

Secondary malignancies may contribute to non-relapse-related mortality among adolescents, young adults, and children who are survivors of cancer, as well as among older survivors of cancer (Armstrong et al. 2009; Liao et al. 2013; Chao et al. 2019; Deng et al. 2022). The development of secondary malignancies is associated with various factors, including treatment factors, environmental exposure, lifestyle factors, and genetic susceptibility. Additionally, the type and age at the time of onset of primary malignancies may be related to their development (Travis et al. 2006; Dracham et al. 2018). Compared to children who are survivors of cancer, older cancer survivors often have risk factors that contribute to the cancer pathogenesis (Demoor-Goldschmidt and de Vathaire 2019; Laconi et al. 2020). Therefore, clarifying the direct relationship between the treatment of primary malignancies and the development of subsequent malignancies is difficult, particularly among older patients. Furthermore, diagnostic methods that can clearly distinguish whether subsequent malignancies are secondary (radiation-induced) malignancies are currently unavailable (Murray et al. 2014).

Table 1. Clinicopathological characteristics of patients in the secondary non-muscle-invasive bladder cancer and control groups (n = 1,019).

	N (%)		P-value
	Control group (n = 993)	Secondary NMIBC group (n = 26)	
Age, years			
< 70 (n = 459)	456 (45.9%)	3 (11.5%)	0.0005
≥ 70 (n = 560)	537 (54.1%)	23 (88.5%)	
Sex			
Male (n = 838)	812 (81.8%)	26 (100%)	0.016
Female (n = 181)	181 (18.2%)	0 (0%)	
Tumor stage			
Ta (n = 678)	659 (66.5%)	19 (73.1%)	0.64
Tis (n = 25)	24 (2.4%)	1 (3.8%)	
T1 (n = 314)	308 (31.1%)	6 (23.1%)	
Tumor grade (WHO 2004/2016)			0.48
Low (n = 388)	379 (48.5%)	9 (40.9%)	
High (n = 416)	403 (51.5%)	13 (59.1%)	
Tumor grade (WHO 1973)			
G1 (n = 104)	102 (13.0%)	2 (9.1%)	0.76
G2 (n = 459)	447 (56.9%)	12 (54.5%)	
G3 (n = 245)	237 (30.1%)	8 (36.4%)	
Tumor multiplicity			
Solitary (n = 490)	478 (49.2%)	12 (52.2%)	0.78
Multiple (n = 504)	493 (50.8%)	11 (47.8%)	
Largest tumor diameter, cm			
< 3 (n = 765)	745 (79.8%)	20 (95.2%)	0.067
≥ 3 (n = 201)	200 (20.2%)	1 (4.8%)	
Presence of CIS			
No (n = 884)	863 (87.2%)	21 (80.8%)	0.34
Yes (n = 132)	127 (12.8%)	5 (19.2%)	
2019 EAU risk groups			
Low (n = 115)	114 (11.5%)	1 (3.8%)	0.12
Intermediate (n = 356)	350 (35.2%)	6 (23.1%)	
High (n = 548)	529 (53.3%)	19 (73.1%)	

CIS, carcinoma in situ; EAU, European Association of Urology; NMIBC, non-muscle-invasive bladder cancer; WHO, World Health Organization.

A recent systematic review and meta-analysis of patients with prostate cancer revealed that patients who received RT may be at a higher risk of developing bladder cancer than those who did not, even after adjusting for multivariable factors (adjusted HR, 1.67) (Wallis et al. 2016). Boorjian et al. (2007) analyzed the CaPSURE™ disease registry and reported that patients with prostate cancer who smoked at the time of diagnosis had an approximately four-fold higher risk of developing bladder cancer when they underwent RT than non-smoking patients who did not receive RT. However, the differences in the incidences of subsequent malignancies, including bladder cancer, may be attributed to the selection bias between patients who underwent surgical treatment and those who underwent RT (Kendal et al. 2007; Hegemann et al. 2017). Moreover, the RT techniques used for treatment may have influenced the incidence of bladder cancer. Huang et al. (2011) performed a matched-pair analysis of patients with prostate cancer with minimal differences in age and the follow-up period and compared the differences in the incidences of subsequent malignancies between patients who underwent surgical treatment and those who underwent RT. In their study,

Table 2. Numbers and proportions of patients in the secondary non-muscle-invasive bladder cancer and control groups who received adjuvant intravesical therapy and underwent a second transurethral resection (n = 1,019).

	N (%)		*P*-value
	Control group (n = 993)	Secondary NMIBC group (n = 26)	
Induction-only BCG			
Yes (n = 273)	262 (26.9%)	11 (42.3%)	0.082
No (n = 726)	711 (73.1%)	15 (57.7%)	
Maintenance BCG			
Yes (n = 150)	143 (14.7%)	7 (26.9%)	0.083
No (n = 849)	830 (85.3%)	19 (73.1%)	
IPIC			
Yes (n = 766)	749 (75.7%)	17 (66.7%)	0.23
No (n = 250)	241 (23.3%)	9 (33.3%)	
Additional adjuvant intravesical chemotherapy			
Yes (n = 121)	121 (12.4%)	0 (0%)	0.055
No (n = 878)	852 (87.6%)	26 (100%)	
Second transurethral resection			
Yes (n = 151)	147 (14.8%)	4 (15.4%)	0.93
No (n = 868)	846 (85.2%)	22 (84.6%)	

BCG, bacillus Calmette–Guérin; IPIC, immediate postoperative instillation of chemotherapy; NMIBC, non-muscle-invasive bladder cancer.

Table 3. Numbers and proportions of patients with secondary non-muscle-invasive bladder cancer and control patients after propensity score-matched analysis who received adjuvant intravesical therapy and underwent a second transurethral resection (n = 54).

	N (%)		*P*-value
	Control group (n = 36)	Secondary NMIBC group (n = 18)	
Induction-only BCG			
Yes (n = 18)	11 (30.6%)	7 (38.9%)	0.54
No (n = 36)	25 (69.4%)	11 (61.1%)	
Maintenance BCG			
Yes (n = 11)	6 (16.7%)	5 (27.8%)	0.34
No (n = 43)	30 (83.3%)	13 (72.2%)	
IPIC			
Yes (n = 38)	25 (69.4%)	13 (72.2%)	0.83
No (n = 16)	11 (30.6%)	5 (27.8%)	
Additional adjuvant intravesical chemotherapy			
Yes (n = 5)	5 (13.9%)	0 (0%)	0.097
No (n = 49)	31 (86.1%)	18 (100%)	
Second transurethral resection			
Yes (n = 5)	3 (8.3%)	2 (11.1%)	0.74
No (n = 49)	33 (91.7%)	16 (88.9%)	

BCG, bacillus Calmette–Guérin; IPIC, immediate postoperative instillation of chemotherapy; NMIBC, non-muscle-invasive bladder cancer.

only two-dimensional RT showed a significant association with the development of subsequent bladder cancer (HR, 2.97), whereas intensity-modulated RT (IMRT) or three-dimensional confocal RT (HR, 0.83) and brachytherapy (HR, 0.66) were not associated with the development of subsequent bladder cancer. Among the 26 patients in the secondary NMIBC group in the present study, 25 underwent EBRT. Of these 25 patients, 12 received IMRT; how-

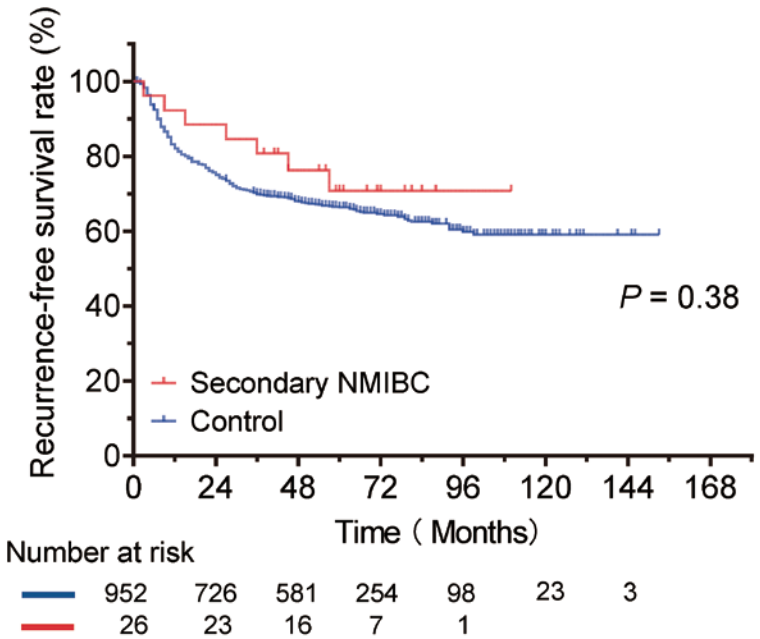

Fig. 1. Kaplan-Meier curves of the RFS of patients in the secondary NMIBC and control groups.
NMIBC, non-muscle-invasive bladder cancer; RFS, recurrence-free survival.

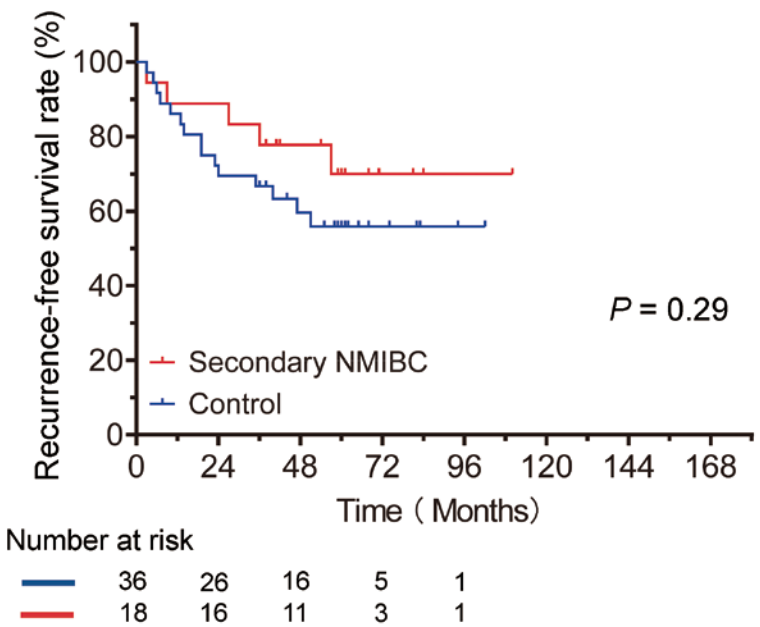

Fig. 2. Kaplan-Meier curves of the RFS of patients with secondary NMIBC and propensity score-matched control patients.
NMIBC, non-muscle-invasive bladder cancer; RFS, recurrence-free survival.

ever, the details of the RT treatment techniques used for the remaining 13 patients were unknown.

Ionizing radiation induces cell death via direct tissue injury, which leads to DNA breaks and free radical production, resulting in oxidative damage (indirect effect) (Huang and Zhou 2020). Radiation-induced genetic alterations of normal cells are the basis for the development of secondary (radiation-induced) malignancies. In addition, the genetic background of the host and total irradiation dose may be associated with radiation-induced tumorigenesis. However, the detailed mechanisms underlying the development of secondary malignancies have not yet been elucidated (Braunstein and Nakamura 2013). In general, a long latent period exists between radiation exposure and the development of these malignancies (Khanna et al. 2021). The relative risk of subsequent malignancy development in patients

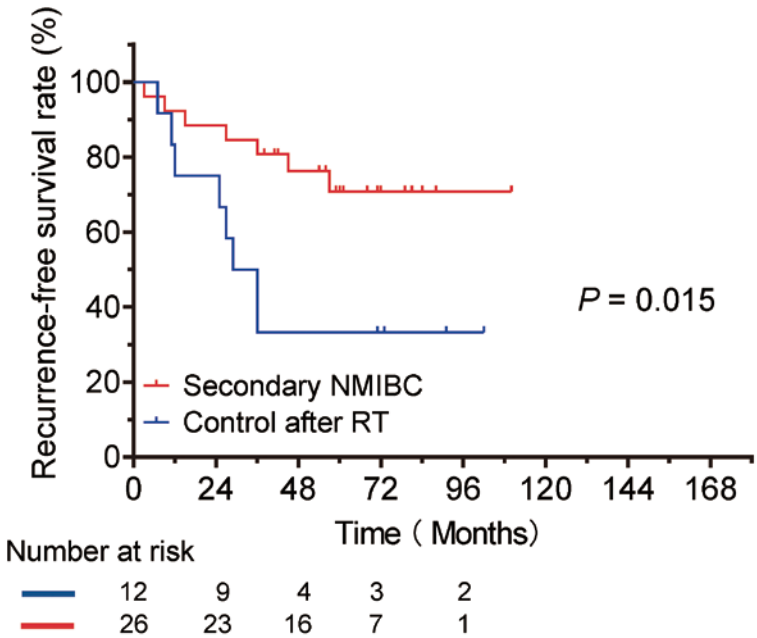

Fig. 3. Kaplan-Meier curves of the RFS of patients in the secondary NMIBC and control after RT groups. NMIBC, non-muscle-invasive bladder cancer; RFS, recurrence-free survival; RT, radiotherapy.

with prostate cancer who received RT increases over time, and this risk continues to increase > 10 years after treatment (Huang et al. 2011). However, the incidence rate of subsequent bladder cancer development after RT for prostate cancer according to the time since RT has not been analyzed in detail. In the present study, newly diagnosed NMIBC that developed ≥ 5 years after RT for prostate cancer was defined as secondary NMIBC. However, proving the validity of the current definition is difficult. In our study, 38 patients who developed newly diagnosed NMIBC after RT for prostate cancer were included, and the median duration between RT and bladder cancer development was 7 years (IQR, 4-9 years; range, 1-12 years). When the analysis was limited to patients who developed NMIBC ≥ 5 years after RT for prostate cancer (n = 26), the median duration between RT and bladder cancer diagnosis was 8 years.

Secondary malignancies that develop after RT may be associated with a poorer prognosis than that of the corresponding primary malignancies; however, this association depends on the histopathological stage and the presence of metastasis (Khanna et al. 2021). Yee et al. (2010) reported that patients who developed bladder cancer after RT for prostate cancer had a significantly higher grade of cancer and experienced progression to a higher stage of disease than those who developed bladder cancer after receiving treatments other than RT for prostate cancer. Although the difference was not significant, a trend toward poorer bladder cancer-specific survival was observed among patients who developed bladder cancer after receiving RT for prostate cancer. Abern et al. (2013) conducted a retrospective analysis of patients with localized prostate cancer reported in the Surveillance, Epidemiology, and End Results (SEER) database and revealed that those who received RT were 1.70 times more likely to develop bladder cancer than those who underwent radical prostatectomy alone. Additionally, the bladder cancer-specific survival of patients who developed bladder cancer after RT for prostate cancer was significantly poorer than that of patients who developed bladder cancer after undergoing radical prostatectomy alone. A retrospective single-institution analysis of patients with bladder cancer who underwent radical cystectomy revealed that those with a history of RT for prostate cancer before bladder cancer development exhibited significantly poorer overall survival and bladder cancer-specific survival than those of matched controls after adjusting for age and stage (Bostrom et al. 2008). Therefore, the findings of these three studies suggested that a history of RT for prostate cancer is associated with poor clinical outcomes of patients with bladder cancer; however, these findings differed from those of our study (Bostrom et al. 2008; Yee et al. 2010; Abern et al. 2013). These aforementioned studies included patients with NMIBC, MIBC, and metastatic bladder cancer and those who developed bladder cancer < 5 years after RT for prostate cancer. Additionally, in the first two studies, bladder cancer-specific survival was compared between patients who developed bladder cancer after RT and those who developed bladder cancer after therapies other than RT for prostate cancer. The aforementioned factors may have contributed to the differences between the results of previous studies and those of our study. However, the detailed mechanisms have not yet been elucidated. In the present study, RFS was similar between patients in the secondary

Table 4. Univariate and multivariate Cox regression analyses results (n = 978).

	Univariate analysis			Multivariate analysis		
	HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value
Age, years						
< 70	Ref.			Ref.		
≥ 70	1.40	(1.13-1.74)	0.0026	1.39	(1.09-1.80)	0.0096
Sex						
Female	Ref.			Ref.		
Male	1.09	(0.82-1.45)	0.53	1.07	(0.76-1.52)	0.70
Tumor stage						
Ta	Ref.			Ref.		
Tis	0.67	(0.30-1.52)	0.34	0.55	(0.13-2.37)	0.42
T1	0.89	(0.70-1.14)	0.36	0.83	(0.59-1.16)	0.26
Tumor grade (WHO 2004/2016)						
Low	Ref.			Ref.		
High	0.94	(0.74-1.20)	0.63	0.91	(0.68-1.22)	0.53
RT history						
No	Ref.			Ref.		
Yes	1.41	(0.77-2.57)	0.27	1.13	(0.47-2.69)	0.79
Tumor multiplicity						
Solitary	Ref.			Ref.		
Multiple	1.34	(1.08-1.68)	0.0078	1.59	(1.24-2.05)	< 0.001
Largest tumor diameter, cm						
< 3	Ref.			Ref.		
≥ 3	1.59	(1.24-2.04)	< 0.001	1.58	(1.15-2.17)	0.0051
Presence of CIS						
No	Ref.			Ref.		
Yes	0.84	(0.60-1.19)	0.33	1.03	(0.65-1.63)	0.91

CI, confidence interval; CIS, carcinoma in situ; HR, hazards ratio; Ref., reference; RT history, a history of radiotherapy for prostate cancer ≥ 5 years before the development of primary non-muscle-invasive bladder cancer; WHO, World Health Organization.

NMIBC and control groups after propensity score matching; however, propensity score matching was performed using only clinicopathological characteristics as the matching factors, without including second TUR and intravesical therapy in the matching process. A trend toward better RFS was observed in patients in the secondary NMIBC group (Figs. 1, 2). In addition, no patient in the secondary NMIBC group experienced disease progression or underwent definitive therapy. However, the present study lacked data on patients who experienced disease recurrence after the initial TURBT followed by the development of progression. Therefore, our data could not be used to estimate the number of patients who developed progression. The RFS of the patients who developed NMIBC < 5 years and ≥ 5 years after RT for prostate cancer were compared in this study. A significant increase in RFS was observed in the latter group (Fig. 3). However, no adjustments were made for clinicopathological factors, and the number of cases in both groups was very small, which decreases the reliability of the statistical analysis.

Tumor characteristics associated with intravesical recurrence (for example, tumor stage, tumor grade, presence of CIS, tumor multiplicity, and largest tumor diameter) were similar between patients in the secondary NMIBC and control groups in our study (Table 1) (Sylvester et al. 2006). Additionally, the proportions of patients who underwent a second TUR or received adjuvant intravesical therapy were similar between groups (Tables 2, 3). A multivariate Cox regression analysis revealed that a history of receiving RT for prostate cancer ≥ 5 years before bladder cancer development was not significantly associated with RFS (HR, 1.13; P = 0.79). However, age (≥ 70 years), tumor multiplicity, and largest tumor diameter (≥ 3 cm) were identified as independent prognostic factors for RFS (Table 4). Therefore, when the analysis was limited to patients with NMIBC, our findings indicated that bladder cancer that developed ≥ 5 years after RT for prostate cancer did not appear to be more aggressive than bladder cancer that did not meet the criterion for secondary NMIBC. However, further studies of larger sample size of patients with MIBC and metastatic

bladder cancer are necessary to confirm this finding.

Various characteristics, such as obesity, chronic inflammation, androgen receptor signaling, and genetic factors (for example, mutations in *TP53*, *RB1*, and *FGFR3*), can contribute to the tumorigenesis of bladder and prostate cancers (Lopez-Beltran et al. 2017). These factors may significantly affect the carcinogenesis of bladder cancer that develops < 5 years after RT for prostate cancer. However, whether the disease course and the process of carcinogenesis differ between patients who developed bladder cancer < 5 and ≥ 5 years after RT for prostate cancer has not been sufficiently investigated. As reported previously, the RFS of patients with bladder cancer who had a history of androgen deprivation therapy for prostate cancer was better than that of patients who did not receive androgen deprivation therapy (Izumi et al. 2014). The present study did not include data on whether patients in the secondary NMIBC and control after RT groups received RT combined with androgen deprivation therapy. However, no patient in the secondary NMIBC group underwent androgen deprivation therapy after bladder cancer diagnosis.

This study had some limitations. First, this was a retrospective study that analyzed patients who did not receive a standardized follow-up regimen. Second, smoking history of the patients, symptoms that resulted in the detection of secondary NMIBC, and location of the tumor within the bladder were not collected during this study. Additionally, the analysis did not include information regarding the primary malignancy (prostate cancer), including the histological type, tumor stage, disease course, precise irradiation field, and additional treatments other than RT for prostate cancer. Regardless of these limitations, this study revealed the clinicopathological characteristics and RFS of patients who developed secondary bladder cancer after RT for prostate cancer.

In conclusion, our study suggested that the RFS and tumor characteristics of patients who developed secondary bladder cancer ≥ 5 years after RT for prostate cancer were similar to those of controls. However, the number of included patients with secondary bladder cancer was very small and the present study lacked sufficient statistical power to detect significant findings. Therefore, further large-scale studies should be performed to clarify the clinicopathological features and outcomes.

Acknowledgments

We thank Drs. Narihiko Kakoi, Takanari Sakai, Rie Sakagami, Masahiro Takahashi, Yuichi Ishizuka, Yosuke Arakawa, Takuya Inoue, Shigetoshi Maiya, Sadafumi Kawamura, Kazuhiko Orikasa, Atsushi Kato, Takudai Takahashi, Taro Akai, Tomoya Yamada, Shingo Kimura, Tomonori Sato, Teppei Okubo, Shin Sato, Maiko Yamashita, Natsuho Hayashi, Daigo Chiba, and Kunihisa Nezu for performing data curation.

Author Contributions

Takuma Sato: Conceptualization, data curation, formal analysis, funding acquisition, writing – original draft, and writing – review and editing. Takeshi Sano: Data curation and writing – review and editing. Hisanobu Adachi: Data curation, resources, and writing – review and editing. Yoshihiro Ikeda: Resources; writing – review and editing. Jun Takemoto: Resources and writing – review and editing. Shingo Myoen: Resources and writing – review and editing. Koji Mitsuzuka: Data curation, resources, and writing – review and editing. Atsushi Kyan: Resources and writing – review and editing. Hiroshi Aoki: Resources and writing – review and editing. Satoru Tokuyama: Resources and writing – review and editing. Hideo Saito: Resources and writing – review and editing. Shinichi Yamashita: Writing – review and editing. Yoichi Arai: Conceptualization and writing – review and editing. Takashi Kobayashi: Resources and writing – review and editing. Akihiro Ito: Supervision and writing – review and editing.

Funding

This work was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (grant number: 18K16721).

Conflict of Interest

The authors declare no conflict of interest.

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